



NIDA Addiction Treatment Discovery Program

2006 Guide for Compound Submitters

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NIDA Capabilities in Medications Discovery & Development

In response to the expanding epidemic of drug addiction in the 1980s, and fueled by the appearance of “crack” cocaine and the continued availability of heroin, the United States Congress mandated the formation of a Medications Development Program (MDP) within the National Institute on Drug Abuse (NIDA). Formed in 1990, the MDP serves to coordinate and encourage academic, private, and federal regulatory involvement in developing and bringing to market new medications for the treatment of drug addiction. Through the MDP, NIDA provides access to preclinical and clinical NIDA contract resources, usually at no cost to academic and private sector partners, to facilitate related medications discovery and development efforts. The MDP also provides scientific consultations to companies that are considering medications development projects related to drug addiction treatment.

NIDA’s efforts have resulted in three successful New Drug Applications to date. Most notably, the MDP played a key role in developing buprenorphine and buprenorphine/naloxone products that were approved by the FDA in 2004 for the treatment of opiate addiction. The MDP’s successes in the opiate field have allowed NIDA to shift its efforts, increasing support for the discovery and development of cocaine and methamphetamine addiction treatments. It has been estimated that there are 2 million current cocaine users and 1.2 million current users of methamphetamine and related stimulants in the United States alone, and there are no approved medications for treating these addiction disorders. Fortunately, there is scientific rationale for pursuing specific biochemical targets, and several of these targets are already the focus of pharmaceutical industry efforts related to clinical indications other than drug addiction treatment. In addition, some compounds hold the promise of addressing relapse and its precipitating stimuli, or so-called “triggers,” that appear common to all drug addiction disorders. Such medications may prove useful not only for treating cocaine and methamphetamine addiction, but also for smoking cessation, for the treatment of alcoholism and marijuana addiction and, correspondingly, for the treatment of polydrug abuse and addiction.

The Addiction Treatment Discovery Program

The Addiction Treatment Discovery Program (ATDP) was created in 2005 through the merger of three separate discovery programs that were focused exclusively on cocaine, opiates, and methamphetamine. A major goal of the earlier programs was the discovery of “agonist therapies” to facilitate quit attempts in cocaine and methamphetamine dependence (such agonist therapies would be analogous to the use of nicotine for smoking cessation). Uncharacterized compounds were accepted into the programs and their pharmacology was characterized through a fixed series of *in vitro* and *in vivo* screens under NIDA contracts. In contrast, the ATDP has shifted focus to emphasize the discovery of compounds aimed at the clinical endpoint of relapse prevention; accordingly, the sequence of testing and related decision trees have evolved. In most cases, the ATDP no longer accepts uncharacterized compounds for

initial *in vitro* testing under NIDA contracts. Instead, the ATDP accepts compounds from specific pharmacological classes and for which there is preliminary data. Compounds of known pharmacology are profiled in relevant animal models, which will vary depending upon the compound's mechanism of action. Because of the focus on relapse prevention as a clinical endpoint, the program has a number of reinstatement models using different drugs of abuse. The ATDP has increased resources to evaluate compounds in models of relapse to cocaine, heroin or methamphetamine, using stress, conditioned cues, or drug primes to produce reinstatement in rats whose self-administration behavior has been extinguished. Compound testing is shaped by existing data in rodents and the sequence of testing is determined in collaboration with the compound submitter.

ATDP staff coordinate testing for compound submitters and provide related study reports and feedback. To ensure confidentiality of data, contracted test sites are blinded to both the source and identity of test compounds. In addition to the relapse models mentioned above, established tests that could be selected for a particular compound include *in vitro* receptor assays, rodent locomotor activity testing, rodent and/or primate drug discrimination testing, rodent and/or primate drug self-administration testing. In addition, a series of predictive toxicology tests – such as the hERG channel assay to predict QT prolongation and the Spot Ames test to predict mutagenicity – are available and, as necessary, additional animal models may be established. NIDA ATDP staff members welcome opportunities to discuss specific testing proposals with potential compound submitters and to present NIDA's capabilities to pharmaceutical company management.

Preclinical & Clinical Development

Medications discovery resources of the ATDP are only one component of the NIDA Medications Development Program, which has contracts to support every aspect of drug development, from GMP synthesis and standard preclinical safety testing to Phase I through III clinical trials. However, NIDA is not in the business of marketing medications and although capable of all aspects of medication development, NIDA does not wish to undertake the full medications development process on its own. Therefore, NIDA seeks to enter into collaborative agreements with private sector partners as early as possible in any development project. As collaborative agreements are established, the relative contributions of each party are negotiated on a case-by-case basis and a formal agreement is drafted.

Confidentiality & Intellectual Property Issues

Information designated as confidential by compound submitters, such as compound structure and identity, is available on a need-to-know basis only to NIDA extramural program personnel associated with the Medication Development Program in Rockville, Maryland. Members of NIDA's Intramural Research Program in Baltimore, Maryland (scientists who may have the goal of synthesizing and patenting potential medications) do not have access to the confidential information and data obtained or generated by the ATDP. The ATDP assigns code numbers to all test compounds, and NIDA-contracted laboratories that conduct pharmacological testing receive compounds only under these code numbers; thus, ATDP test sites are blinded to both the identity and the source of compounds that they receive. Along with the compounds, test sites receive storage and solubility information that is necessary for testing. NIDA ATDP contractors are legally required to treat as confidential any and all compound-related data or other information, whether provided by NIDA or generated during the course of testing. In addition, NIDA ATDP contracts contain a special clause that prevents contractors from claiming rights to data generated under their contracts, protecting the intellectual property rights of compound submitters. Formal agreements for confidential disclosure, screening agreements, clinical trial agreements and cooperative research and development agreements are available and can be developed for the particular needs of the specific collaboration. Compound submitters who desire a formal confidentiality agreement should contact NIDA ATDP staff.

Opportunities for Pharmaceutical Companies

Pharmaceutical companies may utilize NIDA ATDP contract resources to support compound profiling in animal models relevant to addiction or, if company resources can support such testing, NIDA ATDP staff are available to serve in a consultant role during the discovery and development process. Confidentiality agreements are available to cover the transfer of information to NIDA and all consultations are free of charge. For promising compounds that advance from discovery to development, the relative contributions of NIDA and company partners to collaborative drug development projects are negotiated on a case-by-case basis. Historically, NIDA's partners have agreed that GMP synthesis, dosage form development, and manufacturing are best covered by the companies that would ultimately manufacture and market the medications. On the other hand, NIDA has the unique expertise to plan and conduct special preclinical and clinical drug interaction studies to establish the safety of potential medications in the presence of drugs of abuse. NIDA also has the expertise to conduct clinical efficacy trials in drug abusing populations and NIDA has historically covered these areas in its past collaborations with industry. Thus, responsibilities for standard safety testing, both preclinical and clinical (Phase I), with associated pharmacokinetic studies, have been the primary areas of negotiation and are usually decided on the basis of timing or other non scientific factors. NIDA is flexible in this area and sensitive to company development timelines and other issues that may affect a development project.

Opportunities for Chemistry/ Drug Discovery Companies

Mergers or partnerships between companies that have chemical library synthesis/supply capabilities and companies that have library screening capabilities have allowed the first steps of drug discovery to begin outside of traditional pharmaceutical companies. Such companies often license a series of hits or leads to pharmaceutical companies for further development. For addiction-relevant targets, chemistry/drug discovery companies may wish to consider applying for NIDA grant funds to support the initial drug discovery process (see Program Announcement at <http://grants2.nih.gov/grants/guide/pa-files/PAS-06-066.html>). Alternatively, library screening and initial steps toward lead optimization may be conducted with internal company resources, with NIDA assisting with relevant behavioral pharmacology profiling, predictive toxicology evaluations, and/or early preclinical safety assessment under NIDA contracts. For promising and novel compounds, NIDA contracts may be used to support full preclinical development in support of an IND. Because NIDA contract funds are more limited than grant funds, NIDA would encourage companies that qualify as U.S. small businesses (see below) to consider applying for set-aside small business grant funds to support activities such as lead optimization and preclinical development. All of the above options may be discussed with NIDA ATDP staff.

Special Opportunities for Small Businesses

U.S. small businesses having no more than 500 employees may be eligible to obtain substantial funds in support of drug discovery and development from NIDA through Small Business Innovation Research (SBIR) or Small Business Technology Transfer (STTR) grants (see <http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf>). These grants allow for drug development activities in two phases. Recognizing that the usual limitations on funding for the first phase (\$100,000) and the second phase (\$750,000) are incompatible with drug development, NIDA has established a special Program Announcement to support SBIR/STTR Phase II competing continuation awards. Thorough competing continuations, a small business may obtain up to an additional 3 years and an additional \$3,000,000 of support for a project, which may include chemistry, pharmacology, toxicology, and clinical studies. This NIDA Special Program announcement can be found at <http://grants.nih.gov/grants/guide/pa-files/PA-03-154.html>.

Businesses that wish to seek SBIR or STTR grant funds in support of medications development for drug addiction disorders are encouraged to contact NIDA ATDP staff prior to the application process. Guidance from NIDA related to such details as the likely required duration of clinical efficacy trials and the need for special, FDA-required preclinical drug interaction studies to establish the safety of potential medications in the presence of drugs of abuse may be beneficial even to companies that have extensive experience with the standard aspects of drug development. Given the opportunity, NIDA ATDP staff will provide comments and advice on draft grant applications prior to submission to the NIH.

Collaborations with Chemists in Academia & Non-Profit Organizations

NIDA grant funds are available to chemists who wish to pursue medicinal chemistry related to addiction-relevant targets. Chemists are encouraged to partner with pharmacologists so that both synthesis and initial screening may be conducted under one grant. For a related Program Announcement with set-aside funds, see <http://grants2.nih.gov/grants/guide/pa-files/PAS-06-066.html>. Subsequent to the discovery of a lead compounds, chemists are encouraged to work closely with NIDA ATDP staff to utilize ATDP contract resources to assist in the lead optimization process. Predictive toxicology testing (such as the hERG assays to predict QT-prolongation and the spot Ames tests to predict mutagenicity) require relatively small amounts of test material and the resulting data may be extremely useful in selecting a successful development candidate. From a safety perspective, these assays are used to select the most promising lead from a series of compounds in discovery. Evaluation of lead compounds in animal models of addiction may be supported by a grant, by NIDA ATDP contract resources, or both.

Compounds of Special Interest

NIDA-supported basic research has revealed multiple receptor targets, neural circuits, biochemical pathways, and cognitive processes of potential relevance to the development of medications for the improved treatment of drug addiction disorders. Accordingly, the NIDA ATDP is not focused on one specific target, but is instead facilitating medications discovery at a number of targets. In some cases, new medications acting at these targets may fill specific gaps in current treatment options by addressing the absence of approved medications to treat either cocaine or methamphetamine addiction and in other cases, new medications may have broader application in the treatment of polydrug abuse and addiction. The NIDA ATDP would be interested in evaluating compounds that are selective for these targets; however, when considering the individual targets/mechanisms listed in this section, it should be noted that selectivity for one target is not essential and that a compound that has activity at more than one of the listed targets, may be of value. For example, one of the most promising medications for treatment of cocaine addiction is modafinil (Dackis et al., 2005), a compound that may act by attenuating GABAergic transmission (Tanganelli et al., 1992), enhancing glutamatergic transmission (Ferraro et al., 1997), and modulating the reuptake of biogenic amines in specific brain areas (Ferraro et al., 1996; Gallopin et al., 2004). Evidence for the interaction of a single compound with more than one desirable target may be an important finding, and NIDA ATDP staff would be extremely interested in discussing the potential evaluation of such compounds.

CRF-1 Receptor Antagonists

The role of Corticotropin-Releasing Factor (CRF) in drug addiction and the rationale for development of CRF-1 receptor antagonists as treatments for drug dependence have been extensively reviewed (Koob, 1999; Stewart, 2000; Sarnyai et al., 2001). Most encouragingly, in rat models of stress-induced relapse to drug use, CRF-1 antagonists have been shown to block footshock-induced reinstatement of responding for cocaine (Erb et al., 1998; Shaham et al., 1998), heroin (Shaham et al., 1997; Shaham et al., 1998), and alcohol (Le et al., 2000). These data suggest efficacy of CRF-1 antagonists in counteracting the widely acknowledged ability of stress to trigger relapse to multiple drugs of abuse. Such efficacy in multiple drug addiction disorders would be beneficial because abuse and addiction to a single compound is less common than polydrug abuse and addiction.

Multiple pharmaceutical companies have been working toward the development of CRF-1 antagonists for the treatment of depression and/or anxiety. Despite this fact, NIDA received no responses when it actively solicited proposals for a Cooperative Research and Development Agreement (CRADA) partnership related to CRF-1 antagonist development/addiction treatment. It seems likely that this failure to respond to NIDA was simply a reflection of the safety failures that have plagued the development of this class of drugs. The NIDA Medications Development Program remains committed to facilitating the development of a CRF-1 antagonist for the treatment of drug addiction and would welcome private sector partnership when a developable compound is identified. Evaluation of such a compound in stress-induced relapse models within the ATDP would be a logical first step.

CB-1 Receptor Antagonists

Evidence that cannabinoid-1 (CB-1) receptor antagonists may prove useful in treating drug addiction disorders has been the subject of two recent reviews (Le Foll and Goldberg, 2005; Beardsley and Thomas, 2005). Particularly notable in these reviews is the ability of CB-1 receptor antagonists to modulate the pharmacology of THC, nicotine, cocaine, methamphetamine, opiates, and ethanol, which has generated a high level of interest in this class of compounds. Unlike compounds that block the ability of stress to trigger drug-seeking behavior in animal models of relapse, CB-1 antagonists act either by blocking the subjective/rewarding effects of drugs like THC, or by blocking the ability of conditioned cues to promote reinstatement of drug-seeking behavior in animals extinguished from drug self-administration. Rimonabant, a CB-1 antagonist that appears to have inverse agonist properties (Pertwee, 2005), may soon be marketed for the treatment of obesity and available for clinical study. A possible goal for medicinal chemists working toward the discovery of “second generation” compounds is the discovery of neutral CB-1 antagonists. Because it is possible that such compounds would demonstrate improved tolerability in drug-addicted populations, the NIDA ATDP would be interested in evaluating neutral CB-1 antagonists in relevant animal models of addiction.

Orexin Receptor Antagonists

The potential significance of orexin receptors (hypocretin receptors) as targets for the discovery of addiction treatment medications is best considered in the context of the rationale for pursuing CRF-1 and CB-1 antagonists (see above). It is noteworthy that the orexins appear to participate in the hypothalamo-pituitary-adrenal axis, with orexins mediating “hyperarousal” and “overactivation of emotional systems” following stress (Pañeda et al., 2005). Further, Winsky-Sommerer et al. (2004) have demonstrated that orexin-containing neurons in the lateral hypothalamus are innervated by CRF-containing nerve terminals and that stress-induced activation of c-fos in orexin-containing neurons is impaired in mice that are deficient in CRF-1 receptors. It follows that orexin receptor blockade may produce effects that are similar to CRF-1 receptor antagonism. In addition, CB-1 receptors and orexin-1 receptors appear capable of heterodimerization, with CB-1 receptor activation sensitizing orexin-1 receptors to activation by orexin A (Hilairt et al., 2003). If some CB-1 antagonist effects are mediated through the blockade of endocannabinoid-facilitated orexin receptor activation, then direct antagonism of orexin receptors may produce similar effects. Thus, the NIDA ATDP would welcome opportunities to evaluate orexin antagonists in animal models of stress-induced relapse to drug use and in models of conditioned cue- and drug prime-induced relapse. Harris et al. (2005) have demonstrated that the orexin 1 receptor antagonist SB 334867 blocks the expression of morphine conditioned place preference, suggesting an attenuated response to conditioned cues. In addition, SB 334867 has been shown to block footshock-induced reinstatement of cocaine self-administration behavior (Boutrel et al., 2005). Further studies of this class of compounds in animal models of addiction are warranted.

Kappa-Opioid Receptor Antagonists

The concept of a protracted abstinence syndrome following withdrawal from chronic *mu*-opiate use is a well-known phenomenon characterized by dysphoric mood state (Himmelsbach, 1943; Martin, 1984). This dysphoric state may contribute to relapse, in that one possible reason for resumption of *mu*-opiate use is the desire to ameliorate dysphoria with a euphorogenic drug. The hypothesis that the dysphoria of the protracted abstinence syndrome results from an upregulation of the endogenous *kappa*-opioid system (Rothman, 1992) is consistent with studies suggesting that chronic *mu*-opioid agonist treatment upregulates *kappa*-opioid receptors in mice (Gulati and Bhargava, 1988) and enhances behavioral responsivity to *kappa*-opioid agonists in primates (Craft and Dykstra, 1992). Administration of *kappa*-opioid agonists in man is associated with dysphoria and psychotomimetic effects (Kumor et al., 1986; Walsh et al., 2001), which is also consistent with the proposed role of dynorphin, the endogenous *kappa*-opioid agonist, in mood states associated with protracted abstinence. Taken together, these findings suggest that *kappa*-opioid receptor antagonists may block dysphoria experienced during protracted abstinence and, in turn, this may decrease the likelihood of relapse.

While the above rationale is specific for the potential usefulness of *kappa*-opioid antagonists in treating addiction to heroin and other *mu*-opioids, recent studies have demonstrated a role for the *kappa*-opioid system in the response of animals to stress, expanding the potential application

of *kappa*-opioid antagonists to the treatment of cocaine and other drug addiction disorders. Most notably, the *kappa*-opioid antagonists nor-BNI and JDTic have been shown to block stress-induced potentiation of cocaine conditioned place preference (McLaughlin et al., 2003) and to block footshock-induced reinstatement of cocaine self-administration behavior (Beardsley et al., 2005), respectively. The ability of a drug to prevent stress from triggering relapse has important implications for the treatment of polydrug abuse and addiction. With the support of NIDA contracts, JDTic is currently in preclinical development and it is hoped that the compound will advance to clinical testing. The NIDA ATDP is open to the evaluation of additional *kappa*-opioid antagonists, especially those with associated private sector support for co-development with NIDA.

Glutamate Modulators

Reported interactions of virtually all drugs of abuse with glutamatergic systems in brain provide strong rationale for the pursuit of several related biochemical targets in NIDA's medications discovery and development efforts. Tzchentke and Schmidt (2003) have reviewed glutamatergic mechanisms in addiction, emphasizing: 1) a role for glutamate in stimulating dopamine systems related to reward and 2) a dopamine-independent role for glutamate in altering the effects of conditioned stimuli on behavior. It has been proposed that the hallmark of addiction - an unmanageable motivation to take drugs - results from pathological changes in prefrontal-accumbens glutamate transmission (Kalivas et al., 2005).

Data supporting a role for both group I and group II metabotropic glutamate receptors in addiction have been extensively reviewed by Kenny and Markou (2004). A rationale for pursuing mGluR5 antagonists as addiction treatments is supported by the results of mGluR5 knockout studies (Chiamulera et al., 2001) and by reported effects of the mGluR5 antagonist MPEP on self-administration of cocaine, nicotine, and alcohol (Chiamulera et al., 2001; Kenny et al., 2003; Paterson et al., 2003; Olive et al., 2005). Additionally, a rationale for pursuing mGluR2/3 agonists is supported by the efficacy of LY379268 in rat models of cue-induced relapse to cocaine (Baptista et al., 2004) and heroin (Bossert et al., 2005). Two other potentially promising mechanisms of glutamate modulation for addiction treatment are AMPA receptor antagonism (Cornish and Kalivas, 2000; Backstrom and Hyytia, 2004) and NAALADase inhibition (Slusher et al., 2001). The NIDA MDP currently has a number of glutamatergic modulators in clinical development and, therefore, additional glutamate modulators will only be pursued by the ATDP if they possess unique activities or characteristics. Because the list of ongoing development projects is dynamic, potential compound submitters may wish to contact NIDA ATDP staff to determine the level of interest in specific types of glutamate modulators.

GABA-Mimetics

Evidence suggests a role for GABA-B receptor agonists and indirect GABA agonists such as vigabatrin (a GABA-transaminase inhibitor) and NNC-711 (a GABA uptake inhibitor) in the pharmacological treatment of addiction to cocaine and other drugs of abuse. For example,

preclinical studies have found that the GABA-B agonists baclofen and CGP 44532 reduce cocaine self-administration in the rat at doses that have minimal or no effect on food-maintained responding (Roberts et al., 1996; Shoaib et al., 1998; Brebner et al., 1999; Brebner et al., 2000). This finding with baclofen and cocaine has been extended to include other drugs of abuse, including heroin (Xi and Stein, 1999), nicotine (Corrigall et al., 2000; Fattore et al., 2002) and ethanol (Daoust et al., 1987; Colombo et al., 2000). Vigabatrin has been shown to block cocaine- and nicotine-induced conditioned place preference (Dewey et al., 1998; Dewey et al., 1999) as well as cocaine self-administration in the rat (Kushner et al., 1999). A rationale for how GABA-B agonists produce the above effects has been proposed based on the finding that GABA-B receptor agonists inhibit mesolimbic dopamine neurotransmission (Dewey et al., 1999). To the extent that the mesolimbic dopamine system has been implicated in mediating the rewarding effects of drugs of abuse (Wise, 1984), this inhibitory effect of GABA-B receptor agonists on dopamine activity could explain the attenuation in the reinforcing effects of cocaine and other drugs of abuse produced by direct and indirect GABA-B agonists (Dewey et al., 1997; Dewey et al., 1999; Ashby et al., 1999; Gerasimov et al., 1999). Taken together, these findings suggest a role for GABA-B receptors in attenuating the reinforcing effects of a number of different drugs of abuse and GABA-mimetic drugs might therefore be considered as potential broad-spectrum antagonist therapies for drug addiction. In addition, it is noteworthy that vigabatrin blocks increases in nucleus accumbens dopamine caused by cocaine-associated cues (Gerasimov et al., 2001). This suggests that GABA-mimetics may have an important second mechanism of action in treating drug addiction; they may also be effective against cue triggers of relapse.

Results of a 160-subject, NIDA-sponsored efficacy trial of baclofen for the treatment of cocaine addiction will be available in early 2006. In addition, NIDA hopes to initiate an efficacy trial of vigabatrin for the treatment of cocaine addiction in the near future. Correspondingly, the NIDA ATDP will limit itself to evaluating GABAergic compounds with rationale for improved efficacy or tolerability compared to baclofen and vigabatrin. An example of such a compound would be a GABA-transaminase inhibitor that lacks potential for causing the visual field defects seen in a subset of patients receiving vigabatrin (Kalviainen and Nousiainen, 2001).

Dopamine D-1 Receptor Agonists

There is converging evidence that D1 receptors are important targets for therapeutic intervention in cocaine dependence. Dopamine D1 receptors are downregulated by cocaine self-administration in primates (Moore et al., 1998), and D1 receptor agonists have been shown to block both cocaine priming (Self et al., 1996) and initiation of cocaine self-administration in rodents (Self et al., 1996; Caine et al., 1999). In squirrel monkeys trained to self-administer cocaine, D1 agonists blocked or attenuated the effects of different priming doses of cocaine on reinstatement (Khroyan et al., 2003). Finally, a D1 agonist administered intravenously to humans in a proof of concept study was reported to blunt the subjective effects of smoked cocaine and to decrease cocaine craving (Haney et al., 1999).

Dopamine D1 receptors, like dopamine itself, are implicated in the effects of a number of drugs of abuse, including alcohol (Eiler et al., 2003; Tupala and Tiihonen, 2005), morphine (Verma

and Kulkarni, 1995), nicotine (Bahk et al., 2002), and methamphetamine (Worsley et al., 2000; Tong et al., 2003), however, only a few studies have evaluated the effects of D1 agonists on reinstatement or drug taking behavior. Those that have been published have shown that D1 agonists can dose-dependently decrease self-administration of ethanol in mice (Ng and George, 1994) and rats (Cohen et al., 1999).

The effects of D1 agonist on cognition are also of interest and are suggestive of other mechanisms by which D1 agonists may be useful treatments. Deficits in working memory are associated with dopamine dysregulation in the prefrontal cortex and have been extensively studied in experimental paradigms relevant to the cognitive deficits of schizophrenia. In a number of studies, it has been shown that D1 agonists produce improvements in working memory function in primate and rodent models (see review by Goldman-Rakic et al., 2004). In light of the identification of working memory deficits that interfere with treatment in both methamphetamine (Simon et al., 2000) and cocaine abusers (Simon et al., 2002), it is possible that D1 agonists may be beneficial for 1) reducing drug use, 2) preventing relapse, and 3) for improving drug-induced cognitive deficits. These effects could also be found for multiple drugs of abuse, suggesting that a D1 agonist treatment would be highly desirable.

Available D1 agonists remain undeveloped because of a number of unsuitable characteristics, including dosage form issues, poor bioavailability, short half-life, genotoxicity, and/or a lack of receptor selectivity. Chemical library screening efforts by the MDP were unsuccessful in discovering novel D1 agonists that might have characteristics more suitable for clinical development, but the mechanism remains a high priority, and D1 agonists lacking unsuitable characteristics would be of much interest to the ATDP.

Dopamine D-3 Receptor Agonists & Antagonists

Dopamine D3 receptor ligands as potential treatments for drug abuse have been the subject of several recent reviews (Sokoloff et al., 2001; Heidbreder et al., 2005; Joyce and Millan, 2005; Newman et al., 2005). These receptors were cloned in 1990 (Sokoloff et al., 1990) and have been of particular interest to drug abuse researchers in part because they are selectively located in brain regions that are affected by drug abuse (Sokoloff et al., 1990), and are up-regulated in the brains of cocaine overdose fatalities (Mash, 1997). Agonists of these receptors produce behavioral effects in rodents that do not resemble stimulants (Geter-Douglass et al., 1997), but are perceived as cocaine-like by rodents and primates (Acri et al., 1995; Spealman, 1996). The potency of compounds that activate D3 receptors is related to their ability to decrease cocaine self-administration in rats, suggesting the involvement of these receptor types in cocaine drug-taking (Caine et al., 1997). In addition, dopamine D3 partial agonists have been shown to block the behaviorally activating effects of cues that have been paired with cocaine in rats, suggesting potential usefulness in blocking relapse following contact with environmental cues associated with drug use (Pilla et al., 1999).

Dopamine D3 antagonists have been reported to block nicotine-primed reinstatement of nicotine self-administration in rats (Andreoli et al., 2003) as well as cocaine-primed cocaine

seeking in rats (Di Ciano et al., 2003; Gilbert et al., 2005). A D3 antagonist has also been reported to dose-dependently block footshock-induced reinstatement of cocaine self-administration in rats (Xi et al., 2004), overall suggesting a potential role for D3 antagonists in preventing two triggers of relapse. A D3 antagonist has also been shown to block enhancement of electrical brain stimulation reward by cocaine (Vorel et al., 2002), and D3 antagonists have been reported to block both the acquisition and expression of nicotine (Le Foll et al., 2005), cocaine (Vorel et al., 2002), and heroin (Ashby et al., 2003) conditioned place preference in rats. Taken together, results from different laboratories using different behavioral endpoints and different compounds suggest that both dopamine D3 partial agonists and D3 antagonists may be useful treatments, and may be effective for more than one drug of abuse. Dopamine D3 receptor ligands remain a high priority for acquisition and development by the ATDP.

Compounds Inhibiting Reuptake or Stimulating Release of Biogenic Amines

Analogously to the use of nicotine replacement therapy for smoking cessation and the use of *mu*-opioid agonist for treatment of heroin addiction, it has been suggested that stimulant addiction may be treated by medications inhibiting reuptake or stimulating release of biogenic amines (Rothman et al., 2000; Howell and Wilcox, 2001). Briefly, it has been proposed that cocaine and methamphetamine withdrawal - which is characterized by hypoactive dopaminergic, noradrenergic, and/or serotonergic systems - can motivate continued drug use, and that “agonist therapies” acting to indirectly stimulate biogenic amine receptors may normalize brain function and break the cycle of drug use. This hypothesis has driven medications discovery and development efforts for more than a decade and has received substantial support from NIDA. Clinically available compounds, including marketed antidepressants and appetite suppressants, have been evaluated in clinical trials with primarily negative results, and numerous chemistry grants have been awarded to support the synthesis of novel compounds that act indirectly to stimulate biogenic amine receptors. In support of the hypothesis, one of the most promising medications for the treatment of cocaine addiction at this time appears to be modafinil, and one of its pharmacological actions is modulation of biogenic amines.

Given the substantial efforts that have already been devoted to compounds targeting biogenic amine reuptake and release, future drug development efforts involving this mechanism will require substantial justification or unique compound attributes. Chemists seeking support for continued work in this area may wish to focus on the discovery of uptake inhibitors with novel, theoretically desirable transporter selectivity profiles (McCann et al., 2003) or on the discovery of compounds with novel NE, DA and 5-HT releasing profile. Notably, compounds lacking effects on NE reuptake or release but having equivalent effects on DA and 5-HT reuptake or release would be unique and of interest to the NIDA ATDP for profiling in preclinical contracts. Advancement of such compounds to development will likely require compelling data in animal models of addiction.

VMAT-2 Inhibitors

In contrast to cocaine, which increases the levels of extra-synaptic neurotransmitters by inhibiting biogenic amine reuptake at membrane transporters, the actions of amphetamines (e.g., d-amphetamine and methamphetamine) are considerably more complex, suggesting additional medication targets, such as the CNS-specific vesicular monoamine transporter (VMAT2). Amphetamines, like cocaine, inhibit the reuptake at biogenic amines at their cell surface transporters; however, unlike cocaine, amphetamines also function as competitive substrates that are transported into nerve terminals (Sonders et al., 1997), and amphetamines have the additional ability to enter the cell by passive diffusion across the membrane (Fischer and Cho, 1979). Once inside the cell, amphetamines promote displacement of nearby vesicles to the cell membrane and promote exocytotic, calcium-dependent release of transmitter into the extracellular space, which is thought to result from the ability of amphetamines to alkalinize vesicular contents (Mundorf et al., 1999). In addition to promoting exocytosis from vesicles near the cell membrane, amphetamines reach vesicles at a greater distance from the cell surface and cause vesicular leakage of biogenic amines into the cytosol through both alkalinization and interactions with the VMAT2. At the VMAT2, amphetamines bind to the tetrabenazine site, block reuptake of biogenic amines into the vesicle, and promote release of biogenic amines into the cytosol, where the neurotransmitters are available for extracellular release through reversal of the cell membrane transporters (Sulzer et al., 1995).

There is experimental evidence that compounds interacting with the tetrabenazine-binding site on the VMAT2, such as lobeline, have the ability to functionally antagonize the neurochemical and behavioral effects of amphetamine and methamphetamine (Dwoskin and Crooks, 2002). Lobeline not only blocks the discriminative stimulus effects of methamphetamine in rodents (Miller et al., 2001), it also reduces methamphetamine self-administration (Harrod et al., 2001). The NIDA MDP has an ongoing lobeline development project for the treatment of methamphetamine dependence; however, the compound has not reached clinical efficacy testing and the ATDP is interested in evaluating additional compounds acting at this site. It is noteworthy that lobeline shows appreciable affinity for nicotinic receptors. Compounds showing greater selectivity for the VMAT2 may be desirable.

Muscarinic M₅ ACh Receptor Agonists & Antagonists

The unique distribution of muscarinic M₅ ACh receptors (M₅ receptors) in brain and their apparent ability to modulate dopaminergic neurotransmission in brain areas relevant to the reinforcing effects of drugs are noteworthy. While M₅ receptors represent only 2% of all muscarinic receptors in brain (Yasuda et al., 1993), they represent the only muscarinic receptor subtype found on dopaminergic neurons of the substantia nigra and the ventral tegmental area (Vilario et al., 1990; Weiner et al., 1990). Dopaminergic transmission from these midbrain neurons via projections to the nucleus accumbens has long been hypothesized to mediate the reinforcing effects of most drugs of abuse, including cocaine, amphetamines, opiates, ethanol, and nicotine (Roberts et al., 1977; Gessa et al., 1985; Di Chiara G. and Imperato, 1988).

Lacking selective ligands for muscarinic ACh receptor subtypes, researchers investigating the role of these receptors in normal physiology as well as their possible significance to drug abuse and addiction have relied on receptor knockout studies. Mice deficient in M5 receptors show a reduced responsiveness to morphine (Basile et al., 2002) and cocaine (Fink-Jensen et al., 2003) in conditioned place preference studies, suggesting a decrease in the reinforcing properties of these drugs. Decreased sensitivity to cocaine in M5 receptor-deficient mice has been confirmed in recent cocaine self-administration studies; however, it should be noted that this decreased sensitivity was apparent only at low to moderate unit doses of cocaine (Thomsen et al., 2005). M5 receptor-deficient mice show attenuated withdrawal symptoms after prolonged morphine treatment and subsequent naloxone administration (Basile et al., 2002) and they show attenuated cocaine withdrawal-associated anxiety, as measured in an elevated plus-maze (Fink-Jensen et al., 2003).

The likelihood of compensatory neuroadaptations during development cautions against drawing firm conclusions from the above-mentioned knockout studies; however, the results are intriguing and argue for evaluation of selective M5 receptor agonist and antagonists in animal models relevant to drug addiction. Such studies will be critical for understanding the role of M5 receptors in drug addiction disorders and for determining the merits of related medications development efforts.

ORL-1 Receptor Agonists

The opiate receptor-like (ORL)-1 receptor shares a high degree of sequence homology with *mu*-, *delta*- and *kappa*-opioid receptors. Identified in 1994 by molecular cloning with PCR primers to conserved regions within the opiate receptor gene family, the ORL-1 receptor was initially an “orphan receptor” (a receptor with no known endogenous ligand or function). In 1995, two laboratories independently discovered the 17 amino acid peptide that serves as the endogenous agonist for the ORL-1 receptor; this neuropeptide agonist was named “nociceptin” by one laboratory and “orphanin FQ” by the other. Although it is structurally related to the opioid peptide dynorphin A, nociceptin does not bind to any of the traditional opiate receptors. Likewise, the traditional opioid peptides do not activate the ORL-1 receptor and most small drug molecules (including naloxone and naltrexone) that bind to traditional opiate receptors do not show appreciable affinity at the ORL-1 receptor. Substantial evidence has accumulated to support a role for the nociceptin/ORL-1 receptor system in opposing the antinociceptive effects of traditional opioid agonists. Correspondingly, there has been great interest in the potential development of ORL-1 receptor antagonists as analgesics. While nociceptin was initially thought to have pronociceptive activity (Meunier et al., 1995; Reinscheid et al., 1995), the results of subsequent studies (Mogil et al., 1996) suggest that blockade of stress-induced analgesia was responsible for the related findings. Consonant with an ability to oppose stress, nociceptin has demonstrated positive effects in preclinical screens for anxiolytic activity (e.g. Jenck et al., 1997) and knockout mice lacking the nociceptin gene exhibit increased susceptibility and impaired adaptation to stress (Koster et al., 1999).

Given the established efficacy of naltrexone in treating alcohol dependence and the apparent ability of the nociceptin/ORL-1 receptor system to functionally oppose many effects of traditional opioid agonists, several laboratories have evaluated ORL-1 receptor agonists in animal models of alcoholism, with promising results (Martin-Fardon et al., 2000; Kuzmin et al., 2003; Ciccocioppo et al., 2003; Ciccocioppo et al., 2004). Nociceptin and/or the synthetic ORL-1 receptor agonist Ro 64-6198 have been shown to: 1) block the reinforcing effects of ethanol in both conditioned place preference and self-administration studies; 2) block the ability of ethanol to reinstate ethanol conditioned place preference; 3) block the ability of conditioned cues to reinstate ethanol self-administration behavior; and 4) block the ability of a footshock stressor to reinstate ethanol self-administration behavior. While many of the observed effects are similar to those seen with naltrexone, the ability of nociceptin to block stress-induced reinstatement suggests a potential advantage of ORL-1 agonists over naltrexone, in that naltrexone is inactive in this model (Le et al., 1999).

The evaluation of ORL-1 agonists in animal models relevant to other drug dependence disorders has been less extensive and, in some cases, studies have yielded confusing results. For example, while both nociceptin and Ro 64-6198 block the acquisition of morphine conditioned place preference and block morphine-induced reinstatement of this conditioned place preference following extinction (Sakoori and Murphy, 2004; Shoblock et al., 2005), the only published study of ORL-1 agonist effects on opiate self-administration revealed a failure of nociceptin to block heroin self-administration (Walker et al., 1998). It seems unlikely that nociceptin blocks the reinforcing effects of morphine but not those of heroin. One possible explanation for the reported lack of effect on heroin self-administration is that nociceptin blocks the reinforcing but not the sedative effects of heroin; the Walker et al. self-administration study was conducted under conditions in which naloxone, which blocks both the reinforcing and sedative effects of opiates, produced a substantial increase in responding for heroin. A similar increase in responding for heroin following nociceptin pretreatment may have been precluded by heroin-induced sedation. Studies of heroin self-administration that use slightly different methods (e.g., a study with repeated testing after ORL-1 agonist pretreatment in an attempt to achieve extinguished responding) may reveal a blockade of heroin's reinforcing effects.

Evaluation of ORL-1 agonists in self-administration models of stress-, cue- and drug prime-induced relapse is another area that deserves increased attention. It has been reported (Martin-Fardon et al., 2000) that nociceptin fails to prevent footshock-induced reinstatement of cocaine self-administration behavior at i.c.v. nociceptin doses that effectively prevent footshock-induced ethanol self-administration behavior; however, the duration of reinstatement test sessions was 60 minutes for the cocaine rats and just 30 minutes for the ethanol rats. The possible short duration of nociceptin's actions following i.c.v. administration must be taken into consideration. To date, nociceptin is the only ORL-1 agonist that has been evaluated in drug self-administration relapse models. The ATDP would welcome the opportunity to thoroughly profile the effects of synthetic, long-acting ORL-1 agonists - especially those under consideration for development as treatments for alcohol dependence - to gain a better understanding of their potential utility in treating polydrug abuse.

Compounds with Submitter-Documented Rationale

While the above list of medications discovery targets with relevance to drug addiction treatment is extensive, it is not comprehensive; instead, the list represents a snapshot of the targets judged by NIDA ATDP staff to have the strongest rationale for pursuit at the time of this writing. Basic research efforts supported by NIDA continue to generate new data that must be taken into consideration, and the relative strength of the rationale for pursuing targets is dynamic. On a regular basis, consideration is given to potential alternative targets based on newly published findings; however, it is recognized that a wealth of unpublished data with relevance to target identification and validation exists within the private sector. The NIDA ATDP is open to pursuing new targets and compound submitters are encouraged to suggest novel compounds for which theoretical rationale can be developed or for which there is supporting preclinical data. Such compounds may include but are not limited to novel anxiolytics and compounds that interact with dopamine systems via novel or unknown mechanisms. Medicinal chemists who wish to apply for NIDA grant funding may propose any medications discovery target, as long as the rationale is fully and convincingly explained within the background section of the application.

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